ACUTE TOXICITY SUMMARY

ARSINE

(arsenic hydride, arsenic trihydride, hydrogen arsenide)

CAS Registry Number: 7784-42-1

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**160 µg/m³**
Critical effect(s)	hemolysis of red blood cells
Hazard Index target(s)	Hematologic

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

Description	colorless gas
Molecular formula	AsH_3
Molecular weight	77.93
Density	2.695 g/L @ 25°C
Boiling point	-55°C
Melting point	-117°C
Vapor pressure	11,000 mm Hg @ 25°C
Flashpoint	not applicable
Explosive limits	upper = 78 % by volume in air (NIOSH Pocket Guide, 1993) lower = 5.1 % by volume in air (NIOSH Pocket Guide, 1993)
Solubility	soluble in chloroform and benzene, slightly soluble in water, ethyl alcohol and in alkalis
Odor threshold	0.5 ppm (NJ Hazardous Substance Fact Sheets, 1993)
Odor description	garlic (AIHA, 1989)
Metabolites	oxidation to As^{3+}, As_2O_3 (Landrigan *et al*., 1982)
Conversion factor	1 ppm = 3.19 mg/m³ @ 25°C

III. Major Uses or Sources (HSDB, 1993)

Processes such as smelting, galvanizing, soldering, and etching, that require the treatment of metal with strong acids, are possible sources of arsine gas. Acid treatment of metals contaminated with arsenic can result in the release of arsine gas. Arsine is used to provide arsenic as a dopant in the semiconductor industry. Combustion of fossil fuels may produce arsine gas.

IV. Acute Toxicity to Humans

Numerous case reports of accidental arsine poisoning exist in the literature, but reliable estimates of concentrations following acute human intoxication do not exist. This is due in large part to the insidious nature of arsine toxicity - arsine is a colorless gas, has a mild odor at low concentrations, produces no mucous membrane irritation, and usually results in delayed symptoms of toxicity (Klimecki and Carter, 1995). In mammalian systems, arsine primarily targets the erythrocyte and causes hemolysis and methemoglobinemia with acute exposure (NRC, 1984). Jaundice, hemoglobinuria, anuria, hepatic and renal damage, anoxia, and anemia are secondary effects resulting from hemolysis. Before the advent of dialysis, there were no reports of patients surviving if renal failure developed (Buchanan, 1962). Other acute symptoms reported include headache, weakness, dizziness, dyspnea, nausea, vomiting, diarrhea, and abdominal cramping (Klimecki and Carter, 1995). Central and peripheral nervous systems may be affected by acute arsine exposure, leading to agitation, disorientation, hallucinations, psychopathologic abnormalities, and peripheral nerve degeneration (Klimecki and Carter, 1995; Frank, 1976). The psychopathologic and peripheral abnormalities are thought to be secondary to the conversion of arsine to arsenate or arsenite. The first signs and symptoms of toxicity, hemoglobinuria and/or nausea, are usually delayed 2 to 24 hours following exposure (Kleinfeld, 1980).

A case report documents hemolytic anemia, hematuria, and renal failure following intermittent exposure to arsine gas over 2.5 hours (Parish *et al*., 1979). Symptoms of gastrointestinal distress, headache, and malaise were also reported following this exposure. The concentration of arsine gas sampled 3 days after exposure was 0.1 ppm (0.3 mg/m^3), but the concentration at the time of poisoning was unknown. Another typical accidental poisoning resulted when 2 men were exposed to arsine gas in a metal smelting works (Coles *et al*., 1969). Symptoms included nausea, vomiting, red urine, generalized aching, shivering, epigastric pain, and jaundice. However, the more severely affected worker developed symptoms within 1 hour of exposure while the other did not develop symptoms for 24 hours. The more severely affected worker developed acute renal failure that required peritoneal dialysis.

In an occupational study, the highest average concentration of arsine recorded in a battery formation area of a battery manufacturing plant was 20.6 µg/m^3 (0.006 ppm) (Landrigan *et al*., 1982). Elevated levels of urinary arsenic were observed in some workers but effects on the hematopoietic system were apparently not examined.

A study by Williams *et al*. (1981) collected personal and area air samples after 2 workers exhibited symptoms of arsine poisoning while restoring a large 19th century painting. Symptoms included headaches, nausea, weakness, vomiting, and red urine. The blank-corrected air concentration of arsine ranged from 0.010 to 0.067 mg/m^3. While these concentrations are below the OSHA PEL 8-hour TWA of 0.2 mg/m^3, the results may indicate that these workers are sensitive responders or that humans in general may be more sensitive to the effects of arsine than experimental animals. However, the air samples may not represent the actual concentration of arsine that caused the symptoms of poisoning in the workers since the workplace air was not analyzed for arsine until after symptoms were reported. The study also notes that ‘appreciable concentrations’ of lead and arsenic were found in the workplace air.

Predisposing Conditions for Arsine Gas Toxicity

Medical: Persons with renal disease and hematologic disorders such as glucose-6-phosphatase deficiency or sickle cell anemia may be at higher risk for adverse effects following arsine gas exposure (Reprotext, 1999).

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

LC_{50} values reported by Gates (1946) are as follows: 120-210 ppm (380-670 mg/m³) for 10 minutes in rats, 110 ppm (350 mg/m³) for 30 minutes in dogs (equivalent to 190 ppm (610 mg/m³) for 10 minutes), and 200-300 ppm (640-960 mg/m³) for 10 minutes in rabbits. An LC_{50} in mice was reported as 31 ppm (99 mg/m³) for a 50-minute exposure (Levvy, 1947). The survival time of the fatalities (4 days) was reported to be more or less independent of exposure concentration (2500 mg/m³ to 25 mg/m³) and exposure duration.

The study by Levvy (1947) varied exposure durations for each given concentration of arsine. Because the mortality data were not presented in conventional form by the standard LC_{50} method, the data were normalized to a 1-hour exposure using Haber's equation ($C^n \times T = K$). The exponent "n" of 1.8 was determined by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. Only 54 data points were used to estimate the exponent n because these points were of sufficient duration ($\geq$ 5 minutes) and resulted in the best chi-square fit for the line and obvious heterogeneity (Table 1).

Table 1. Selected mice mortality results from Levvy (1947) and the 1-hour adjusted concentration using Haber's equation ($C^n \times T = K$, where n = 1.8).

Concentration (ppm)	Exposure Duration (min)	Mortality (no. died/total)	1-Hour Adjusted Concentration (ppm)
157*	10	30/30	58
	5	28/30	39
	2.5	17/30	27
	1.7	0/30	22
78.4*	15	21/30	36
	9	10/30	27
31.4	70	30/30	34
	50	15/30	28

* *Shaded rows include data used for determination of the ED_{05} and BD_{05}*

Craig and Frye (1988) reported a 4-hour LC_{50} of 42.6 ppm in rats. However, when the rats were separated by sex for statistical purposes, there was slightly greater mortality among females than males (38.9 ppm LC_{50} for females vs. 46.8 ppm LC_{50} for males). No abnormalities were seen at necropsy except red discharge from nose, mouth, and genitalia at the higher concentrations. A

concentration-related suppression of body weight gain was observed during the first week of the 14-day post-observation period.

The most comprehensive arsine lethality study was undertaken by IRDC (1985). LC_{50}'s of 240, 178, and 45 ppm were determined in rats (10 rats/sex/group) for 30 minute, 1 hour, and 4 hour exposures, respectively. Deaths generally occurred within 3 days following 30 minute exposure to arsine. As in the previous study (Craig and Frye, 1988), there was slightly greater mortality in females than males. Adverse effects noted during exposure included dyspnea, while effects noted post-exposure included a concentration-related increase in hematuria, dark material around the head or the anogenital area, and pallor of ears, eyes, and feet. The higher concentrations resulted in weight loss immediately following exposure, suppressed weight gain during the first week, and compensatory weight gains during the second week post-exposure. Necropsy on animals that died showed red, yellow or orange fluid in the bladder, stomach, or intestine, and discoloration of the kidneys, lungs, and liver.

Data in the IRDC (1985) report were used to determine the exponent "n" in the equation $C^n \times T = K$. This was done by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. The value of "n" for extrapolation to 1-hour exposure was dependent on exposure duration. For extrapolation from 30 minutes to 1-hour exposure, n = 2.2; for extrapolation from 4-hours to 1-hour exposure, n = 1.0.

Table 2 contains the studies which provided adequate raw mortality data from which a maximum likelihood estimate corresponding to 5% lethality (MLE_{05}) and benchmark dose at the 95% lower confidence interval of the MLE_{05} and MLE_{01} (BD_{05} and BD_{01}, respectively) could be determined.

Table 2. Animal Lethality Benchmark Dose Determinations in ppm for Arsine

Reference	Species	Exposure Time (min)	LC_{50} 60 min[1]	MLE_{05} 60 min[1]	BD_{05} 60 min[1]	BD_{01} 60 min[1]
IRDC, 1985	rat	30	175	120	105	86
	rat	60	178	112	88	66
	rat	240	181	118	101	80
Craig and Frye, 1988	rat	240	170	125	102	84
Levvy, 1947	mice	varied[2]	29	20	16	13

[1] Exposure time was extrapolated to 60 minutes, if needed, using a modification of Haber's equation ($C^n * T = K$). For rats, n = 2.2 for extrapolation from 30 minutes to 1-hour, or n = 1.0 for extrapolation from 4 hours to 1-hour; for mice, n = 1.8.

[2] Lethality data for 5 exposure durations were pooled and normalized to a 1-hour exposure using the equation $C^n \times T = K$ (see Table 1).

In other experimental animal studies, a reduction in hematocrit as a function of arsine concentration was observed in mice following a 1-hour exposure (Peterson and Bhattacharyya, 1985). A LOAEL of 9 ppm (29 mg/m³) and a NOAEL of 5 ppm (16 mg/m³) were reported. The

demarcation between the NOAEL and LOAEL for this non-lethal effect was well defined, not only among the exposure groups (5 ppm vs. 9 ppm), but also among individual mice in each exposure group (Peterson, 1990). Hematologic recovery of the surviving mice was gradual but nearly complete within 11 days after exposure (Peterson and Bhattacharyya, 1985). The study also reported a NOAEL of 15 ppm (100% survival) and LOAEL of 26 ppm (100% lethality) for lethality. Therefore, the NOAEL/LOAEL approach for determination of a severe adverse effect level for arsine is appropriate.

A subchronic study in male and female rats and female mice (Fowler *et al*., 1988) supports the sharp demarcation in dose-response noted by Peterson and Bhattacharyya (1985). All treatment groups exposed to arsine (6 hr/day, 5 days/week) at concentrations of 10 ppm and above showed 100 percent mortality within 4 days while those exposed to 5 ppm or less showed no mortality or overt signs of toxicity. Other effects observed included a dose-related increase in spleen weight and a slight increase in liver weight. Blood samples taken at necropsy showed a slight dose-related decrease in hematocrit and a marked dose-related increase in the activity of red blood cell ALAD (δ-aminolevulinic acid dehydratase).

In a 90 day study, male and female mice were exposed to 0, 0.025, 0.5, and 2.5 ppm arsine gas for 6 hours/day, 5 days/week (Blair *et al*., 1990). After 5, 15, and 90 days, blood was collected for hematologic analysis. Exposure to 2.5 ppm had significant effects on all hematological parameters for nearly the entire exposure period, while 0.5 ppm caused only a few significant changes in hematological parameters at day 90 of exposure (decreased hemoglobin in males and increased MCV in females). Exposure to 0.025 ppm was without effect.

VI. Reproductive or Developmental Toxicity

In an unpublished study, workers in one semiconductor plant were reported to have a 39% rate of miscarriage, almost twice the national average (Sanger, 1987). Workers were exposed to unidentified levels of arsine gas, but other possible exposures were not identified.

A developmental toxicity study exposed pregnant rats and mice to 0.025, 0.5, or 2.5 ppm (0.079, 1.5, or 7.9 mg/m^3) arsine for 6 hours per day on gestation days 6 through 15 (Morrissey *et al*., 1990). The rats exposed to 2.5 ppm exhibited a significant increase in fetal body weight, but no other endpoints of developmental toxicity were observed. The incidence of malformations observed in arsine exposed mice at 0.025 ppm (exencephaly) and at 2.5 ppm (unfused eyelids) was not significantly different from control mice.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Mild Adverse Effect Level

Because lysis of red blood cells is considered a severe adverse effect, and since this effect occurs at or below the threshold for discomfort (a mild adverse effect), there is no mild adverse effect level currently recommended for arsine.

Reference Exposure Level (protective against severe adverse effects): 0.05 ppm (160 μg/m³)

Study	Peterson and Bhattacharyya, 1985; Peterson, 1990
Study population	mice
Exposure method	inhalation
Critical effects	lysis of red blood cells
LOAEL	9 ppm (29 mg/m³)
NOAEL	5 ppm (16 mg/m³)
Exposure duration	1 hour
Extrapolated 1 hour concentration	5 ppm
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	0.05 ppm (0.16 mg/m³; 160 μg/m³)

Level Protective Against Life-threatening Effects

The work by Craig and Frye (1988) and IRDC (1985) provide recent, well-conducted rat lethality studies from which to derive a life threatening level for arsine from human data using the standard benchmark dose approach. However, the results by Levvy (1947) indicate that mice are at least 5-fold more sensitive to the lethal effects of arsine than rats (see Table 2). This finding is supported by the recent study by Peterson and Bhattacharyya (1985), which observed a 1-hour NOAEL and LOAEL for lethality of 15 and 26 ppm, respectively. Therefore, the level for arsine is based on mouse lethality data obtained from Levvy (1947). Based on probit analysis of data by Levvy (1947), a BD_{05} of 16 ppm was determined in mice for 1-hour exposure to arsine. An uncertainty factor of 3 was applied to the BC_{05} to account for interspecies differences because the BD_{05} likely accounts for some degree of variation and an uncertainty factor of 10 was applied to account for increased susceptibility of sensitive human individuals.

$$\text{Level protective against life-threatening effects} = BC/(UF)$$

The total uncertainty factor was 30. Incorporation of these factors results in a level protective against life-threatening effects for arsine of 0.537 ppm (1.712 mg/m³) for 1-hour exposure.

VIII. References

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